

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 23, 2002

FROM: Renan A. Bonnel, Pharm.D., M.P.H., Safety Evaluator  
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director (Signed on 1/23/2002)  
Division of Drug Risk Evaluation, HFD-430

TO: Deborah Liederman M.D., Director  
Division of Controlled Substance Staff  
Office of the Center Director, CDER, HFD-009

SUBJECT: Office of Drug Safety-Postmarketing Safety Review (PID #: D020014)  
Drug : Tramadol (Ultram®, NDA-20281)  
Reaction: Deaths between 3/2/2000-12/31/2001

Confidential: contains IMS data; not to be used outside of the FDA without clearance from IMS.

INTRODUCTION/EXECUTIVE SUMMARY

This consult is in response to Dr. Michael Klein's (CDER, Control Substance Staff-CSS) request to update reports of death in association with tramadol use :

This document is not a comprehensive review and no attempt was made to match duplicate reports or perform individual case evaluations. This review provides crude counts and demographic data of the reports that were received by FDA since the comprehensive review of death cases associated with tramadol was completed on April 21, 2000 by Renan Bonnel from the Office of Drug Safety (ODS, formerly OPDRA).

The Adverse Event Reporting System (AERS) database contains 133 death reports since the last ODS review in 2000. Of those, 126 reports indicated tramadol as a suspect agent. The top event terms include completed suicide and drug overdose. There were 57 females, 67 males and 9 reports with an unknown gender. There was no significant gender difference. The majority of the cases were domestic in origin. The dose, duration, h/o drug abuse, concomitant medications, and cause of death were not evaluated. The demographic data indicate that most patients were middle age adults. The highest number of deaths (33/133-25%) occurred between the ages of 31-40 years old. There were no death reports in individuals under 12 years old.

In summary, the postmarketing reports of deaths in association with tramadol use continue to exist in FDA's AERS database. Completed suicide and drug overdoses are among the top terms

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and constitute a large number of the total death reports. These findings concur with the findings of the ODS 2000 report on tramadol related deaths.

## **PRODUCT INFORMATION AND LABELING**

Tramadol was approved on March 3, 1995 and is presently marketed by Ortho-McNeil Pharmaceuticals for the management of moderate to moderately severe pain. A combination product with acetaminophen (Ultracet) was approved in 2001. During the Ultracet approval process, tramadol (Ultram) labeling was revised to include drug abuse and dependence in the warnings and overdose sections. A sustained release formulation, and pediatric use is currently being evaluated in the U.S.

Tramadol is a centrally acting analgesic that is not derived from natural sources nor is it chemically related to opiates. Although its mode of action is not completely understood from preclinical studies, at least two complementary mechanisms appear applicable: binding to  $\mu$ -opioid receptors and inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to  $\mu$ -opioid receptors. In animal models, M1 is more potent than tramadol in producing analgesia and binding to  $\mu$ -opioid receptors. Human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol is extensively metabolized in the liver by the CYP2D6 P-450 isoenzyme. Therefore, concomitant administration CYP2D6 inhibitors, such as fluoxetine, paroxetine, and amitriptyline or inducers such as carbamazepine could alter tramadol metabolism. Approximately 30% of the dose is excreted in the urine as unchanged drug and 60% of the dose is excreted as metabolites.

There are several **Warnings** in the labeling, including *Seizure risk, Anaphylactoid Reactions, Avoidance of Use in Opioid-dependent Patients, Use with CNS Depressants, and Use with MAO Inhibitors.*

### **Physical Dependence and Abuse:**

Tramadol may induce psychic and physical dependence of the morphine-type ( $\mu$ -opioid). (See **DRUG ABUSE AND DEPENDENCE**) Tramadol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.

There are **Precautions** regarding *Respiratory Depression, Increased Intracranial Pressure or Head trauma, Acute Abdominal conditions, Patients Physically dependent on Opioids, Drug Interactions, Use in Labor and Delivery, Use in the Pediatric Population, and Use in Renal and Hepatic Disease.*

The **Drug Interactions** section of the labeling indicates that concomitant administration with inhibitors of CYP2D6 such as *fluoxetine, paroxetine, and amitriptyline* could result in some inhibition of the metabolism of tramadol. Interactions with *MAO Inhibitors*, due to an interference with the detoxification mechanism, is mentioned in this section as well as the warnings section. Post-marketing findings such as, alterations of *warfarin* effect, including elevation of prothrombin time was stated.

There are also several relevant events listed in the **Adverse Reactions** section of the labeling. They are *Body as a Whole- Anaphylaxis, Allergic reaction; Cardiovascular-myocardial infarction, syncope, hypotension; Respiratory-dyspnea; CNS-Seizures; Gastrointestinal-GI Bleeding; Skin-Stevens-Johnson syndrome/ Toxic epidermal necrolysis; and Lab Abnormalities-Elevated liver enzymes.*

The **Drug abuse and dependence** section of the labeling indicates that Ultram has the potential to cause psychic and physical dependence of the morphine-type ( $\mu$ -opioid). The drug has been associated with craving, drug-seeking behavior and tolerance development. Cases of abuse and dependence have been reported and the label recommends that it should not be used in opioid-dependent patients.

The **Overdosage** section includes the following statements. Cases of *overdose* with tramadol have been reported. The lowest dose reported to be associated with fatality was possibly between 500 and 1000mg. Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS .) Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with tramadol.

## **DRUG USE**

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## **OVERVIEW OF AERS REPORTS**

### **All Reports**

A total of 803 reports (foreign and domestic) for tramadol (Ultram) were entered in AERS between 3/2/2000 to 12/31/ 2001 of which 767 were reported as serious, and 133 had a fatal outcome. This is a crude report count and may include duplicate reports.

The counts of most frequently reported and "relevant" (bolded) PT terms from the total of 803 cases were:

<b>DRUG ABUSER NOS</b>	<b>151</b>
<b>CONVULSIONS NOS</b>	<b>137</b>
<b>DRUG DEPENDENCE</b>	<b>107</b>
<b>DRUG WITHDRAWAL SYNDROME</b>	<b>78</b>
CONFUSION	41
DRUG INTERACTION NOS	40
NAUSEA	30
COMA	26
FALL	26
VOMITING NOS	25
DIZZINESS (EXCL VERTIGO)	24
GRAND MAL CONVULSION	23
TREMOR	23
LOSS OF CONSCIOUSNESS	19
SEDATION	22
HEADACHE NOS	21
MALAISE	21
COMPLETED SUICIDE	20
DISORIENTATION	20

It is noted that drug abuse, drug dependence, drug withdrawal syndrome, and convulsions constitute a large number of terms from the total 803 reports.

### **Death Reports**

Counts of the most frequently reported and "relevant" (bolded) PT terms from the total of 133 death reports are listed below. One report may contain more than one event.

<b>COMPLETED SUICIDE</b>	<b>20</b>
<b>OVERDOSE NOS</b>	<b>17</b>
PULMONARY EDEMA	17
TOXICOLOGY NOS ABNORMAL	15
COMA	14
<b>DRUG LEVEL NOS ABOVE THERAPEUTIC</b>	<b>14</b>
DRUG TOXICITY NOS	14
DRUG INTERACTION NOS	11

ACCIDENTAL OVERDOSE	9
NON- ACCIDENTAL OVERDOSE	9
CONVULSIONS NOS	8
LOSS OF CONSCIOUSNESS	8
SEDATION	7

Completed suicide and overdose cases were among the top terms and constitute a large number of the total death reports.

Twenty-nine cases were foreign, 89 were U.S and 15 were unknown. Fifty-seven were females and 67 were males, and 9 did not report the gender.

The age distribution of the 133 deaths are as follows.

0-11 yrs	0
12-16	1
17-20	1
21-30-	17
<b>31-40</b>	<b>33</b>
41-50	16
51-60	15
61-70	13
71-80	9
81-90	10
91+	1
null age	17

The highest number of deaths occurred between the ages of 31-40 years old.

## **CONCLUSION**

In response to Dr. Michael Klein's (CDER, CSS, HFD-009) request, we evaluated a total of 133 deaths reported with Ultram® (tramadol) use. This document is not a comprehensive review of deaths and no attempt was made to match duplicate reports or perform individual reviews of the cases due to the time limitation. The review provides a crude count and demographic data of the reports that were received by the FDA since 2000.

A total of 133 death reports were entered in the Adverse Event Reporting System (AERS) database since 3/2/2000. Of those, 126 reports indicated tramadol as the suspect agent. The top event terms include completed suicide and drug overdose. There was no significant gender difference. The majority of the reports were domestic in origin.

Because, an evaluation of the individual death reports was not performed, the role of tramadol as well as the dose, duration, h/o drug abuse, and concomitant medications could not be assessed. The highest number of deaths (33/133-25%) occurred between the ages of 31-40 years old. There were no death reports in individuals under 12 years old.

In summary, FDA's AERS database continues to receive postmarketing reports of deaths for tramadol use. The crude report counts indicate that completed suicide and drug overdoses are among the top event terms. These findings concur with the findings of the ODS 2000 evaluation of deaths with tramadol use.

## REFERENCES

1. Ultram® (tramadol) product label. Ortho-McNeil Pharmaceutical. 1999

*Signed on 1/23/2002*

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Renan A. Bonnel, Pharm.D., M.P.H.  
Post-Marketing Safety Evaluator

Concurrence:

*Signed on 1/23/2002*

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Claudia B. Karwoski, Pharm.D.  
Team Leader